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Review

Modern Views on the Phenomenon of Viral Interference and its Role in the Regulation of the Infectious Process

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Abstract

Numerous studies have proven the pronounced mutual influence of both respiratory and intestinal viruses, which is often expressed in the suppression of one virus by another. The mechanism of interference is most often considered from the standpoint of multifactorial, it is related to the stimulation of specific products in infected cells, in particular interferons, which inhibit the replication of other viruses. At the same time, among the mechanisms of viral interference, RNA interference has attracted great interest among researchers. The microRNA system regulates many processes in eukaryotic cells, similar elements have been found in viruses. Viral microRNAs are capable of both enhancing viral infection and suppressing it. At the same time, despite the significant successes of experimental medicine, the mechanisms of viral interference remain not fully elucidated and require further, first of all, fundamental research.

Keywords: viruses, interference, interferons, microRNA

Резюме

Многобройни проучвания са доказали ясно изразеното взаимно влияние на респираторните и чревните вируси, което често се изразява в потискане на един вирус от друг. Механизмът на намесата най-често се разглежда от гледна точка на многофакторността, той е свързан със стимулирането на специфични продукти в инфектираните клетки, по-специално интерферони, които потискат репликацията на други вируси. В същото време, сред механизмите на вирусната интерференция голям интерес сред изследователите предизвиква РНК интерференцията. Системата на микроРНК регулира много процеси в еукариотните клетки, като подобни елементи са открити и при вирусите. Вирусните микроРНК са способни както да засилват вирусната инфекция, така и да я потискат. В същото време, въпреки значителните успехи на експерименталната медицина, механизмите на вирусната интерференция все още не са напълно изяснени и изискват допълнителни, преди всичко фундаментални изследвания.

Introduction

In virology, the term "interference" (from Latin inter – mutual, between, and ferio – strike) can be interpreted broadly – as the interaction of two viruses when one host is affected. However, positive interference may well fit into the concept of co-infection or superinfection and is not the subject of this article. Therefore, in the following, we will use the term "interference" only in the sense of "negative virus interference," i.e., the inhibition of replication of one virus by another (Escobedo-Bonilla, 2021).

The phenomenon of viral interference is an important element of microorganisms' existence, which ensures their adaptation, influences evolution and, of course, is of great importance in the regulation of the infectious process. The phenomenon of viral interference was first described in 1935 when M. Hoskins proved that a monkey infected

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with a neurotropic yellow fever virus became insensitive to the yellow fever virus, which affected the internal organs. For many years, scientists explained this phenomenon by the usual competition between two rival viruses, and the scientist himself believed that the phenomenon he discovered was based on nothing more than a combination of the effects of both pathogens. In the meantime, such an explanation was far from revealing the mechanism of the phenomenon, and the nature of the virus interference phenomenon remained unknown for a long time. Only in 1957, British researcher Alick Isaacs and Swiss Jean Lindenmann made a reasonable assumption about a possible different mechanism of viral interference associated with the production of low molecular weight glycoproteins by infected cells, which we now call interferons, whose inhibitory effect extended to competing viruses even before the synthesis of specific immunoglobulins (Escobedo-Bonilla, 2021; Piret and Boivin, 2022).

The interference between respiratory viruses

At present, the most studied is the interference between respiratory viruses, which today occupy leading positions in the structure of the incidence of viral diseases in the world. The investigation of the seasonal outbreak of influenza in Japan in 1977, when two serotypes of influenza A viruses, H1N1 and H3N2, were circulating at once, is interesting in this regard. The researchers found that the incidence of A(H1N1) in schools that had previously experienced an outbreak of A(H3N2) was lower, which is explained by the formation of natural immunity. However, in the case of a simultaneous outbreak of both infections, the incidence rate decreased even further, which clearly indicates interference between the viruses (Sonoguchi *et al*., 1985). When modeling this situation in ferrets, it was found that the development of infection largely depends on the interval between the administration of different types of influenza viruses. Thus, if the interval was less than three days, coinfection developed, and in the interval from 3 to 7 days, interference weakening of infections was observed. The most powerful inducer of such interference was the pandemic A (H1N1) (Laurie *et al*., 2015).

It also seems that influenza A viruses and respiratory syncytial virus (RSV) have an antagonistic relationship. For example, in Norway, during influenza epidemics, the RS virus was usually isolated less frequently (Anestad *et al*., 2007). In addition, the probability of simultaneous isolation of both viruses was significantly lower than the one mathematically calculated for a random distribution, which in turn may indicate the involvement of viral interference processes.

In a ferret model, researchers also found that infection of these animals with influenza virus effectively blocks the development of respiratory viral infection within 7 days. It is also interesting that the above effect was not observed when animals were initially infected with RSV and then infected with the influenza virus, although the course of influenza infection was much milder and mortality was significantly lower (Chan *et al*., 2018).

Similar results were obtained when analyzing outbreaks of rhinovirus and influenza infection that were close in time. For example, researchers note that in 2009 in Europe and 2014 in Hong Kong, outbreaks of rhinovirus infection significantly reduced or even prevented influenza outbreaks (Casalegno *et al*., 2010; Zheng *et al*., 2017). Other scientists have shown in a mouse experiment that infecting animals with rhinovirus 2 days before the introduction of influenza virus alleviated the course of rhinovirus infection. In contrast, with the simultaneous administration of these pathogens, the effect was significantly weaker and was manifested by a slight inflammation of the upper respiratory tract, which allowed the host to eliminate the influenza virus faster (Wu *et al*., 2020).

In the case of the COVID-19 pandemic, the issue of interference is only beginning to be intensively studied, although there is already scientific evidence that rhinoviruses can interact with SARS-CoV-2, reducing its replication in epithelial cells (Cheemarla *et al*., 2021; Kaidashev *et al*., 2021). Scientists attribute this effect to the expression of interferon-stimulated genes.

No less relevant and interesting is the phenomenon of interference of intestinal viruses. For example, when assessing viral contamination of wastewater, interference between reoviruses and enteroviruses was found. Both pathogens can multiply in the intestine, but the concentration of reoviruses is usually much higher, and can often be up to -lg 1010-12. In this case, the interference was manifested by a significant decrease in the cytopathic effect of polioviruses, to the point where the authors state that it is impossible to correctly assess the number and depth of CPE in the presence of reoviruses. Instead, the reproduction of enteroviruses in cells was productive, as evidenced by positive PCR results (Carducci *et al*., 2002).

The mechanisms of interference

The nature of the interference phenome-

non remains unclear at the moment. Currently, the mechanisms of interference are considered from a multifactorial perspective and are associated with the stimulation of specific products in infected cells that inhibit the replication of other viruses.

The most studied mechanism of interference is the production of interferons. Recognition of certain components of viruses by cell receptors triggers the production of interferons. Interferon alpha and beta receptors are present in most cells, while interferon gamma receptors are found mainly in the epithelial cells of the respiratory tract and gastrointestinal tract. Synthesized interferons bind to the receptors of virus-affected cells and activate interferon-stimulated genes, which trigger mechanisms to block viral replication. Accordingly, if the second virus is a weaker inducer of interferon, its reproduction will be much more limited than in mono-infection (Piret and Boivin, 2022).

To a certain extent, the phenomenon of immunological memory, which is of great importance for the formation of specific immunity, may influence the phenomenon of virus interference. For example, studies in syngeneic mice have demonstrated that the presence of memory T cells stimulated by one virus has a serious impact on the outcome of other viral infections. Experiments have demonstrated this effect for lymphocytic choriomeningitis virus (LCMV), poliovirus, cowpox virus, murine cytomegalovirus, and vesicular stomatitis virus. Moreover, according to the authors, the effect depended on both the nature and the specific order in which the pathogens were encountered (Selin *et al*., 1996). The manifestation of such an immune response can have both positive and harmful consequences (Chen *et al*., 2001). For example, there are reports that antibodies to influenza in mice can protect them from infection with the smallpox vaccine virus. At the same time, this increases the possibility of infection with cytomegalovirus infections (Chen *et al*., 2003). Thus, the memory T-cell pool affects the course of each infection, and with each subsequent infection, the memory of T cells for previously encountered agents changes.

It is also possible that cross-immunity can form when antibodies to one virus can bind to and neutralize related viruses. For example, the phenomenon of cross-immunity is widely known in the flavivirus family. The researchers also report on the effect of already formed antibodies against tick-borne encephalitis and yellow fever viruses on the dynamics of antibody formation to dengue virus. The researchers examined the blood sera of vaccinated and previously infected individuals with tick-borne encephalitis virus and showed a pronounced cross-reactivity of IgG antibodies in approximately 15.1% of the YF vaccinated group and approximately 9.5% of the yellow fever vaccinated group. In total, 15 out of 80 samples (18.8%) had detectable IgG antibody titters to dengue virus. In addition, serum samples from patients with acute tick-borne encephalitis had not only the highest level of antibodies to this virus but were characterized by a pronounced high cross-reactivity directed to dengue virus antigens (Allwinn *et al*., 2002). It is also known that the Zika virus has areas on the envelope that are common to the dengue virus, and since it is the envelope antigens that are the main targets for protective antibodies, the formation of immunity against dengue virus was accompanied by an increase in the activity of neutralizing Zika virus, although only in the short term (Priyamvada *et al*., 2017). Similar effects were observed in the study of arenaviruses. In particular, there is information that monoclonal antibodies obtained against lymphocytic chorionic villous meningitis viruses demonstrated activity against heterologous arenaviruses (Ngo *et al*., 2015).

At the same time, there is scientific evidence that completely excludes the immunological aspects of viral interference. They are mainly related to the study of the phenomenon of superinfection elimination. This type of virus interaction occurs when a primary viral infection causes resistance to subsequent infections with similar viruses. This is the most common type of interference described for bacteriophages, flaviviruses, ortho-myxoviruses, para-myxoviruses, retroviruses, hepatoviruses, arboviruses, and plant viruses. For example, infection of cell cultures with a sublethal or defective interfering virus makes them resistant to infection with a full-fledged cytopathic virus (van Dongen *et al*., 2019). Moreover, the vesicular stomatitis virus only needed one interfering viral particle to completely stop the multiplication of the superinfecting virus, this is the so-called mutual exclusion effect, or "everything or nothing" (Bloyet *et al*., 2020). Out-of-body interference of viruses of different species, such as cowpox and vesicular stomatitis and Sindbis virus with dengue virus in cell cultures, and interference of avian influenza A virus and Newcastle disease in chicken embryos was also observed (Ge *et al*., 2012; Salas-Benito *et al*., 2015).

Based on a large number of studies in this area, researchers (DaPalma *et al*., 2010; Ding *et al*., 2018) identify the following main areas of viral in-

terference: direct interaction of viral genes or gene products; damage in host cellular mechanisms leading to indirect viral interactions and immunological interactions occurring only in the whole organism with a functioning immune system.

We consider the first category to be the most interesting. This includes the physical interaction of the nucleic acids or proteins of one virus with the genes or gene products of another virus. One of the possible mechanisms of such interaction is RNA interference of viruses.

The mechanisms of regulation of cellular processes by microRNAs (miRNAs) have been extensively studied in recent years. MicroRNA was originally discovered in Caenorhabditis elegans and found in most eukaryotes, including humans (Perron and Provost, 2008). The genes responsible for its production are believed to account for up to 5% of the human genome and regulate at least 30% of the protein-coding genes (Stanczyk *et al*., 2008). To date, about 1000 individual microRNAs have been identified in the human genome (Griffiths-Jones, 2006). The detailed pathways of the RNA system in the cell have not yet been elucidated, but it is obvious that they regulate the expression of genes controlling a large number of intracellular processes (Cui *et al*., 2022). MicroRNAs are capable of binding to mRNA, terminating the synthesis of certain protein molecules, and are part of the RNA-induced inhibition system (RISC, RNA-induced silencing complex). The level of complementarity between the microRNA and the target mRNA determines which inhibition mechanism will be used – cleavage of the target (mRNA) with subsequent degradation or inhibition of translation. (Pozniak *et al*., 2022).

MicroRNAs are evolutionarily highly conserved (e.g., shared by insects and mammals) single-stranded non-coding RNA molecules. This high conservatism leads one to believe that this is an evolutionarily very ancient system for regulating processes in eukaryotic cells. MicroRNAs not only regulate endogenous gene expression, they protect the genome from transposon invasion and prevent the integration of viral nucleic acids.

Since microRNAs can effectively regulate the expression of the target gene by inhibiting its transcription and mRNA translation in this regulatory pathway it is possible and even possible that the phenomenon of RNA interference can be compared to create highly effective antiviral drugs. All that is needed, at least theoretically, is to know the sequence of the desired viral protein. A clinical hypothesis then arises about the possibility of using RNA interference to inhibit SARS-CoV-2 reproduction at the stage of early viral protein synthesis.

However, the microRNA phenomenon has another side. As mentioned above, prokaryotic (bacterial cells) do not have such a system, while viruses, despite the small size of their genome, have a microRNA system.

MicroRNAs are potentially ideal tools for viruses to modulate gene expression. Unlike viral proteins, microRNAs are nonimmunogenic, require less coding ability, and can rapidly evolve to target new transcripts. Point mutations in the seed site of the microRNA can alter target specificity, whereas mutations within the pre-miRNA can affect chain loading in the RISC. In addition, microRNAs not only have the ability to target mRNAs with high specificity but can also regulate multiple transcripts to varying degrees. Taking advantage of a conserved gene regulatory mechanism in the host cell, viral microRNAs can help create a cellular environment favorable to viral replication.

Although the role of viral microRNAs is not yet fully understood, it is clear that viral microRNAs can target both viral and cellular transcripts.

Viral microRNAs, like other viral factors, are involved in reprogramming cellular processes in favor of the virus, control stages of latent and lytic infection, maintain viral replication by regulating cell survival, proliferation, and/or differentiation, and can even modulate the immune response. Modulation of the host cell environment is achieved through different and partially overlapping mechanisms, as viral microRNAs and proteins work synergistically to help create a cellular environment favorable to the completion of the virus life cycle (Pozniak *et al*., 2022; Rebecca *et al*., 2010).

Given these unique properties, it is not surprising that a number of viral DNA encode microRNA. Currently, more than 200 viral microRNAs have been identified, predominantly in herpes viruses, but also in polyomaviruses, ascoviruses and adenoviruses. For DNA-genomic viruses, the use of microRNAs is facilitated by the fact that they have access to the cell nucleus since at present viral microRNA biogenesis is thought to be mediated exclusively by cellular factors, since viral proteins involved in microRNA processing have not yet been described. In addition, double-stranded DNA viruses exhibit bidirectional transcription, and therefore specific regulation of the viral transcript sequence is easily achieved by expression of antisense microRNAs. Finally, the unique

ability of DNA viruses, especially herpesviruses, to create long-lasting latent infections means that these viruses must block the host's innate or adaptive immune responses for a long time while minimizing the expression of potentially antigenic viral proteins. However, it should be noted that RNA-genomic viruses can also contain microRNA. Among such viruses, retroviruses, a unique family of complex RNA-genomic viruses that replicate via reverse transcription and integrate a DNA copy of their own genome into the host genome, should be highlighted first. As a consequence, retroviruses are potential RNA viruses for microRNA generation because all retroviral transcription occurs from the host machinery, which is similar to microRNA expression in cells. The first HIV-1 encoded rv-miRNA, miR-N367, has been experimentally identified in mammalian cells infected with the virus (Omoto *et al*., 2004). Researchers report that its expression leads to suppression of HIV-1 transcription, while others (rv-miRNA, HIV-1-miR-H1, miR-140, miR-H3-3p), lead to increased HIV-1 replication (Zhang *et al*., 2014).

At the same time, microRNAs have been found in other RNA-genomic viruses as well, particularly in the influenza virus. Among these viruses the currently most dangerous strain H5N1, known as the "bird flu" pathogen, which is highly pathogenic for birds and highly lethal for humans. The danger of H5N1 in humans is, among other things, associated with increased cytokine levels and hyperactivation of immune cells (cytokine storm), leading to lung damage (Yuan *et al*., 2021). As a result of deep sequencing of the virus-infected cell line, scientists have now managed to identify the H5N1-encoded miR-HA-3p (Li *et al*., 2018). Subsequent studies have shown that this miRNA activates a number of antiviral signaling pathways, including the inflammatory response (Cheng *et al*., 2018). In addition, blocking miR-HA-3p has been shown to inhibit the production of inflammatory cytokines during H5N1 infection both in vivo and in vitro, and the histological indicators of lung damage and mouse survival rates are also improved using the same approach, suggesting a potential therapeutic strategy against H5N1 infection based on rv-miRNA suppression (Li *et al*., 2018).

Similar results were obtained when studying West Nile virus and dengue virus, which are cytoplasmic viruses with a single-stranded plus-RNA genome. Both viruses are mosquito-borne and can cause a range of diseases from mild to fatal with significant public health impacts. A microRNA-like RNA, KUN-miR-1, has been identified using a bioinformatics approach as the first microRNA encoded by cytoplasmic RNA viruses (Hussain *et al*., 2012). It contributes to viral replication. At the same time, the dengue virus microRNA, DENV-vsRNA-5, identified by deep sequencing in DENV-2-infected mosquito cells and in mammalian cells, inhibits viral replication, indicating that microRNA may be used to limit dengue virus replication (Hussain *et al*., 2014).

The presence of microRNAs contributing to virus replication was discovered and then confirmed by numerous studies on the Ebola virus (Hsu *et al*., 2018). The Ebola virus has a single-stranded genome with negative RNA and causes a severe and often fatal disease (Jacob *et al*., 2020). MicroRNAs with the ability to inhibit the virus were preliminarily calculated by computer modeling; however, they proved to be ineffective (Prasad *et al*., 2020).

And, of course, the special interest of the entire scientific community is now confined to the SARS-CoV-2 virus, the causative agent of severe acute respiratory syndrome and intestinal infections in humans and animals, which caused the SARS epidemic in 2003 and the COVID-19 pandemic (Marchenko *et al*., 2021). Currently, scientists using deep sequencing have been able to identify three rv microRNAs in lungs derived from SARS-CoV-infected mice. This study also shows that sv-RNA molecules derived from sites of viral nucleoprotein and nonstructural protein 3 contribute to the pathogenesis of SARS-CoV. In particular, blocking these sv-RNAs resulted in a significant facilitation of the infection (Morales *et al*., 2017). Other experiments using bioinformatics have shown that SARS-CoV-2 encodes several putative rv microRNAs from different regions of the virus genome and targets various signaling molecules involved in apoptosis, immune function, cell cycle, and transcription (Aydemir *et al*., 2021). However, further studies are required to experimentally assess their expression and biological functions in the context of viral infection.

Conclusions

What draws attention in the above cases is the fact that viruses contain microRNAs, which not only aggravate their replication but can also inhibit it. Certainly, as mentioned above, this opens up wide possibilities for the therapeutic use of these molecules. However, within the framework of our article, it should be assumed that it is the presence of microRNAs capable of inhibiting their replication in the viral genome that can be considered as a

new possible mechanism of viral interference and, in the future, contribute to the development of new effective antiviral drugs.

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